REMARKS

In the Office Action dated April 24, 2006, claims 1-44 are pending, of which claims 1-30, 37 and 43 are withdrawn from further consideration as directed to non-elected subject matter. Claims 31-36, 38-42 and 44 are under consideration and are rejected.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The specification is objected to for allegedly failing to comply with the sequence rules set forth in 37 C.F.R. §§1.821-1.825. The Examiner indicates that the specification recites sequences on pages 19 and 24 that are not accompanied by sequence identifiers.

Applicants have amended the specification to include sequence identifiers for the sequences disclosed on pages 19 and 24. In addition, Applicants are providing herewith an initial paper copy and an initial computer-readable copy of a Sequence Listing, which set forth the sequences disclosed on pages 19 and 24 of the specification. A Statement verifying the identity between the paper and computer-readable copies of the Sequence Listing is also enclosed. No new matter is introduced by the amendment to the specification or the Sequence Listing. Withdrawal of the objection to the specification is respectfully requested.

Claims 41 and 44 are objected to for depending from claims that are withdrawn from consideration.

Applicants respectfully submit that claims 41 and 44, as presently amended, do not depend from claims that are withdrawn from consideration. Withdrawal of the objection is respectfully requested.

Claims 41, 42 and 44 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. The Examiner contends that the specification, while enabling for

treating Alzheimer's disease, does not reasonably provide enablement for prevention or alleviation of Alzheimer's disease.

Applicants respectfully submit that in an effort to favorably advance prosecution of the present application, the claims have been amended to delete the terms "prevention" and "alleviation". Applicants reserve the right to pursue subject matter relating to prevention or alleviation of Alzheimer's disease in a continuation application. In view of such amendment, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 31-36, 38 and 39 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Shao et al. (J. Mol. Biology 285: 755-773 (1999); hereinafter "Shao").

According to the Examiner, Shao teaches that the NMR work established that nicotine binds to the His13 and His14 side-chains of the Tyr10-Val24 α-helix, and this prevented an α-helix to β-sheet conversion and β-amyloid precipitation. The Examiner contends that in conducting the NMR, one is inherently practicing the method, as binding of nicotine to β-amyloid protein at His13 and His14 inherently "blocks" the N-terminus in such a way that binding of metal ions at said His residue(s) is inhibited.

In response, Applicants respectfully submit that it is believed that nicotine does not inhibit the interaction of Aβ with metal ions. Nicotine is merely disclosed to interact with the histidine residues of monomeric Aβ in an α-helical conformation, which is a non–physiological form of the peptide. On the other hand, the compounds of the present invention target Aβ in a beta-sheet and random coil conformations in addition to the α-helical conformation. Given that the relative positions of the side chains are different in the various conformations of Aβ, it is unlikely that nicotine would recognize all structural forms of Aβ to effectively inhibit the interaction of Aβ with metal ions.

In this connection, Applicants respectfully draw the Examiner's attention to the fact that the compounds employed in the claimed methods "blocks and destabilizes the N-terminal loop of the peptide, thereby inhibiting the binding of one or more metal ions" to the N-terminus. Shao does not disclose any compound that inhibits metal binding to the N-terminal of Aβ.

Furthermore, Applicants observe that in the context of describing the nicotine binding to Aβ, Shao refers to Salomon et al. for detailed conditions (*Proc. Natl. Acad. Sci.* 94: 4109-4112, 1997, a copy of which is attached as **Exhibit 1**). As disclosed in Salomon at page 13568, second column, second paragraph, the binding experiment is conducted in the presence of sodium phosphate buffer which, of itself, *promotes* a conformation form of the Aβ peptide with poor metal binding properties. Therefore, Applicants respectfully submit that Shao refers to the Salomon article that merely discloses an experimental system incapable of establishing whether a compound could or could not inhibit the binding of metals to Aβ in the first instance.

In view of the foregoing, Applicants respectfully submit that Shao does not teach a method based on the use of a compound that blocks or destabilizes the N-terminal loop of the peptide, thereby inhibiting the binding of one or more metal ions to at least one histidine residue within the N-terminal loop.

Applicants have also added claims 45 and 46 to further define certain preferred embodiments of the present invention. Claim 45 depends upon claim 31 and further defines the method step to be carried out "in the presence of in the presence of at least one metal ion capable of binding the peptide". Support for claim 45 is found throughout the specification, e.g., on page 17, lines 10-17. Applicants respectfully submit that although Shao discloses that nicotine binds His13 and His14 in an NMR study, the reference does not disclose that the binding (performed in the NMR study) took place in the presence of any metal ions that bind Aβ. Claim 46 depends

upon claim 31 and further defines the compound to be a metal complex. Support for claim 46 is found in the specification, e.g., at pages 5,11, and 12. Nicotine is not a metal complex. Therefore, it is respectfully submitted that claims 45-46 are fully supported by the specification and distinguished over Shao.

In view of the foregoing, Applicants respectfully submit that the §102(b) rejection based on Shao is overcome. Withdrawal of the rejection is respectfully requested.

Claims 31-36, 38-42 and 44 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Nordenberg (FDA publication 99-1288, 1999). According to the Examiner, Nordenberg teaches that nicotine is present in cigarettes. According to the Examiner, by smoking or attempting to quit smoking, one inherently practices the instantly claimed methods, as nicotine is delivered into the bloodstream, where it necessarily contacts Aβ protein and inhibits binding of metal ions and/or inhibits aggregation, and would necessarily be "preventing" Alzheimer's disease. Furthermore, the Examiner states that because the instant patient population does not preclude smokers or those quitting, any Alzheimer's patient that smokes, or uses the patch, gum, spray or inhaler, is inherently "treating" and/or "alleviating" Alzheimer's.

In the first instance, Applicants respectfully reassert that it is believed that nicotine is not a compound that can effectively inhibit the binding of one or more metal ions to at least one histidine residue within the N-terminal loop, as discussed above. Therefore, Applicants respectfully submit that Nordenberg does not anticipate the subject matter of the present claims.

Furthermore, with respect to claims 41 and 44, Nordenberg merely suggests giving cigarettes (containing nicotine) to the general public. The reference does not teach providing a relevant compound to a selected population, i.e., subjects suffering Alzheimer's disease, in order

to treat the disease. Therefore, Nordenberg does not anticipate the subject matter of claims 41 and 44.

In addition, with respect to claim 46, Nordenberg does not teach exposing the Aβ peptide to a metal complex. Thus, Nordenberg does not anticipate the subject matter of claim 46.

In view of the foregoing, Applicants respectfully submit that the §102(b) rejection based on Nordenberg is overcome. Withdrawal of the rejection is respectfully requested.

Claims 31-36, 38-42 and 44 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Findeis (U.S. Patent No. 5,854,215).

According to the Examiner, Findeis teaches a method of inhibiting Aβ aggregation with compounds of the general formula A-X, A being a "modulating group" and X being β–amyloid peptide. Findeis additionally teaches treating Alzheimer's Disease with a retro-inverso isomer of Aβ and with Aβ coupled to a modulating group. The Examiner contends that because the compounds disclosed by Findeis meet the structural limitation set forth in the claims and are used in the same method steps, the compound must necessarily have the asserted functions, e.g. blocking metal binding to Aβ.

Applicants respectfully submit that the Examiner has not explained as to how the compounds of Findeis meet the structural limitations of the compound, as recited in the present claims. For example, Applicants respectfully submit that Findeis does not teach that the compounds disclosed therein bind to, thereby blocking, the His residues of Aβ. Although the reference may have disclosed compounds that bind Aβ and reduce the formation of aggregates, these compounds may mediate formation of aggregates by binding to other parts of Aβ (i.e., parts other than Histidine residues). Accordingly, Applicants respectfully submit that Findeis does not

teach a method based on the use of a compound that binds to, thereby blocking, the His residues of Aβ, as presently claimed. Withdrawal of the §102(b) rejection based on Findeis is respectfully requested.

In view of foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Encls: Exhibit 1; Initial paper copy of sequence listing; Initial CRF of sequence listing on disk and Statement under 37 C.F.R. §§1.821(f) and (g).